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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,587	09/06/2001	Antonio Grillo-Lopez	PM0277847	5272

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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,587	GRILLO-LOPEZ, ANTONIO	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 10-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group II, claims 7-9, species intermediate grade NHL in Paper Nos. 8, 10 is acknowledged. The traversal is on the ground(s) that all the groups are directed to related methods for treating B cell lymphoma, that involve the admnistration of anti-CD20 antibody, and that different grades of NHL represent different degrees of progression of a single disease. This is not found persuasive because the technical feature of group I, administration of an anti-CD20 antibody, lacks novelty or inventive step as evidenced by US 5,595721, and does not make a contribution over the prior art. According to PCT rule 13.2 unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group II, claims 7-9, B-cell lymphoma are examined in the instant application.

OBJECTION

1. The specification is objected to because the trademark, e.g. RITUXIMAB on page 8, 9, is not capitalized.

2. Claim 7 is objected to for the use of the language "appreciable" tumor regression, which is a relative term. The specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7-9 are drawn to a method for treating a subject having B-cell lymphoma, which subject has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administrating to said patient a radiolabeled anti-CD20 antibody.

The specification discloses that as reported in US 5,736137, sequential administration of a chimeric anti-CD20 antibody, RITUXIMAB with radiolabeled anti-CD20 antibody is sufficient to clear any remaining peripheral blood B-cells not clear by the chimeric antibody (p.12, third paragraph). The specification discloses that a phase III trial is also being conducted in patients with relapsed NHL who are refractory to RITUXIMAB (p.33-34). No data from the above phase III treatment is found in the specification.

Further, no disclosure is found in the specification concerning any data from treating a subject having B-cell lymphoma, which subject has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administrating to said patient a radiolabeled anti-CD20 antibody.

One cannot extrapolate the teaching in the specification to the claims. It is well known in the art that loss of surface CD20 of B cells from non-Hodgkin's lymphoma

(NHL) could occur after treatment of a patient with anti-CD20 antibody, and recurrent treatment could be prevented by such a loss of CD-20 on tumor cells surface (Davis T et al, 1998, Proceed Amer Assoc Cancer Res Annual meeting, 39, page 435, # 2964).

Further, down regulation or loss of tumor antigen is well known in the art. For example, an effective autochothonuous immune response can convert a Her-2/Neu positive tumor to Her-2/Neu negative (Cheever et al, PN=5,726,023, column 9, first paragraph). Further, White et al, 2001, Ann Rev Med, 52: 125-145, teach that for a successful immunotherapy, besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last).

Thus it is unpredictable that a subject having B-cell lymphoma with intermediate grade NHL, which has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, would not have lost or downregulated surface CD20 of the cancerous B-lymphoma cells. Consequently, it is unpredictable that further treating said patient with a radiolabeled anti-CD20 antibody would be effective, because if surface CD20 antigen is not present or downregulated on B-lymphoma cells, it is unpredictable that the labeled anti-CD20 antibody would bind and kill cancerous B-lymphoma cells.

Further, it is well known in the art that cancer treatment is unpredictable. For example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method for treating a subject having B-cell lymphoma, which subject has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administrating to said patient a radiolabeled anti-CD20 antibody would be effective as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing

effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method for treating a subject having B-cell lymphoma, which subject has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administrating to said patient a radiolabeled anti-CD20 antibody would be effective as claimed. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2).

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph, claims 7-9 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating non-Hodgkin's lymphoma (NHL), does not reasonably provide enablement for a method for treating "any B-cell lymphoma". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 7-9 are drawn to a method for treating a subject having B-cell lymphoma, which subject has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administrating to said patient a radiolabeled anti-CD20 antibody.

The specification discloses that FDA approved RITUXIMAB was based on five single agent studies in patients with low grade and follicular NHL (p.13, last paragraph). The specification further discloses that patients with mantle-cell disease do not respond radiolabeled anti-CD20 antibody (p.34, first paragraph).

Therefore, in view of the disclosure of the specification concerning patients with mantle-cell disease, a B-cell lymphoma, it is unpredictable that any B lymphoma would

be treated with the claimed method, because different diseases have different etiology and characteristics, and they are similar in responding to the drugs.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

June 19, 2003